REMARKS

With the cancellation of claim 9, claims 1-8, 10-12, 14, and 15 are now pending and currently under examination. Claims 9, 10, 11, 12, and 15 were rejected under 35 U.S.C. § 112, first paragraph. Claims 1-8, 11, 12, 14, and 15 were rejected under § 103(a). Each of these rejections is addressed as follows.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 9, 10, 11, 12, and 15 stand finally rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

The test of enablement is whether one reasonably skilled in the art could make and use the invention, relying on the patent specification and the knowledge known in the art. In essence, the Office has rejected the claims on the basis that "Applicants have failed to provide a nexus between results achieved *in vitro* and predictable success *in vivo*" (see Office Action – page 6, end of first paragraph). More specifically, the Office states that "there is no indication in the specification [1] what levels of chemokines would be therapeutic *in vivo*, nor [2] that such a therapeutic level could be attained using the Sendai virus vector, nor [3] that the levels expressed *in vitro* can be correlated to levels of protein expression which can be attained *in vivo*" (Office Action– page 5, top half).

Of the rejected claims, only claim 9 is expressly directed to *in vivo* gene therapy in human subjects. With the cancellation of claim 9, this rejection is moot.

Claim 10 is directed to *ex vivo* gene therapy, a routine, conventional, and predictable procedure. The unpredictability issues raised by the Examiner in the Office Action with respect to *in vivo* gene therapy, such a cell targeting, the regulation of gene expression, and whether sufficient transfection of target cells can be attained to achieve a therapeutic level of chemokine expression, are irrelevant to the claimed method of *ex vivo* therapy. In fact, *ex vivo* cell therapy and recycling of treated cells is common in the treatment of immunosuppressed conditions, such as cancer and HIV.[1] For example, patients routinely undergo autologous bone marrow transplants for the treatment of lymphomas. Likewise, *ex vivo* gene therapy involving cytokine-transduced tumor vaccines has been used to treat breast and prostate cancers (See, for example, Simons, J.W. et al., *Semin. Oncol.* (1998) 25(6):661-676; copy enclosed). Moreover, many autologous cell types have been successfully modified *ex vivo* to deliver recombinant gene products (See, for example, Chang, P.L. et al., *Adv. Drug Deliv. Rev.* (1998) 3:33(1-2):31-43; copy enclosed), using a variety of viral vectors, to treat conditions ranging from Parkinson's Disease (See, for example, Raymon, H.K. et al., *Exp. Neurol.* (1997) 144 (1):82-91; copy enclosed) to Duchenne Muscular Dystrophy (See, for example, Floyd, S.S. et al., *Gene Ther.* (1998) 5(1):19-30; copy enclosed). When the cells used in such treatments are differentiated cells or cells with a limited half-life, repeated treatment may indeed be necessary. However, this neither undermines nor negates the enablement of the method as claimed, involving two basic steps of *in vitro* transfection of cells and the

[1] The references cited herein were identified from a cursory search of the PubMed database using the keywords "*ex vivo* gene therapy" and "viral vector."

return of transfected cells to the body, both of which are amply supported by the specification as originally filed. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Claims 11 and 12 are directed to "pharmaceutical compositions" comprising a chemokine-expressing Sendai virus vector. Here the Office asserts that the specification fails to enable "how to use" such compositions for the reasons given above with regard to *in vivo* gene therapy. However, Applicants note that the Examiner deems the claims of this scope to be "obvious" to one of ordinary skill in the art, based on references whose experimental findings, like those of Applicants, are limited to *in vitro* expression levels (i.e., references that arguably do not "enable" the use of pharmaceutical compositions for the reasons given above). If the claims are obvious to one of ordinary skill in the art from the *in vitro* teachings of Yu and Bluel et al., how can they not be suitably enabled by the present specification, coupled with the teachings of the prior art? The Examiner's rejections appear contradictory. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Claim 15 was also rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This rejection has been met by the present amendment, which limits the claim to "inhibiting proliferation of HIV-infected cells *in vitro*." Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1-8, 11, 12, 14, and 15 stand finally rejected under 35 U.S.C. § 103(a) as obvious over Yu et al. in view of Bluel et al. Yu describes Sendai viral vectors. Bluel describes the expression of chemoattractant SDF-1, a chemokine. The Office Action states "there would have been a reasonable expectation of success by one of ordinary skill in the art to express a chemokine using a Sendai virus vector." Applicants disagree.

The test of obviousness *vel non* is statutory. It requires that one compare the claim's "subject matter as a whole" with the prior art "to which said subject matter pertains." 35 U.S.C. §103(a). The inquiry is fact-specific. This is so "whether the invention be a process for making or a process of using, or some other process." *In re Kuehl*, 475 F.2d 658, 665, 177 U.S.P.Q. 250, 255 (C.C.P.A. 1973). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Fine*, 837 F.2d 1071,1075, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To prevent the use of hindsight based on the invention to defeat patentability, the Federal Circuit requires the Examiner to show a motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). The Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *Id.* When the references cited by the Patent Office fail to establish a *prima*

facie case of obviousness, the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d at 1074, 5 U.S.P.Q.2d at 1598.

As an initial matter, Applicants note that Yu makes no mention of constructing or of using a Sendai virus vector to express a chemokine. Moreover, the Office provides no scientific explanation as to why the gp120 protein that was expressed by Yu using the Sendai virus vector is interchangeable with a Sendai virus vector that expresses a chemokine. There is simply no evidence provided by the Office to support the proposition that the expression of the gp120 protein using a Sendai virus vector reasonably predicts the expression of a chemokine using that system, especially given that the same expression system failed to produce substantial amounts of biologically active luciferase. Absent a logical predicate, it is unreasonable to assume that the expression of a chemokine and a gp120 protein by a Sendai virus vector are equivalent systems. Accordingly, to the extent that the Office relies upon Yu to establish that it would have been obvious to express a chemokine using a Sendai virus vector, merely because it would be obvious to try such an experiment, the Office is in error. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 U.S.P.Q. 81, (Fed. Cir. 1986) *cert. denied*, 480 U.S. 947 (1987). ("Obvious to try" is improper consideration in adjudicating obviousness issue.)

Similarly, a conclusion that the claims are obvious cannot be properly reached when Yu is considered in view of Bluel. Bluel discusses chemokines, and certainly does not discuss in any way expressing a chemokine gene using a Sendai virus. The Office

has indeed acknowledged this fact by stating that "Bluel et al does not teach its [SDF-1, a chemokine] production from recombinant Sendai virus vector."[2] The existence of a reference merely disclosing a chemokine is insufficient, when combined with the Yu article, to support a finding of obviousness. Because Yu is limited to Sendai virus expressing gp120 proteins and fails to teach or suggest expression of a chemokine using a Sendai virus, and further because Bluel fails to suggest or motivate the selection of a Sendai virus vector for expressing a chemokine, the Bluel article does not compensate for the substantial differences between expression of gp120 and luciferase when employing a Sendai virus vector. The Yu and Bluel references in combination therefore cannot support the present obviousness rejection.

Turning to the specific issue raised by the Examiner's conclusion that "there is nothing in the declaration [of Dr. Makoto Inoue] that would lead one to conclude that a polynucleotide encoding any polypeptide would not be expressed when inserted into a Sendai virus vector system" (see Final Rejection – page 9, paragraph 1), Applicants again point out that the issue is not whether or not a protein would be expressed by Sendai virus but whether one in the art would have been motivated to select a Sendai virus vector in view of the teachings of Yu and whether the art established a "reasonable expectation of success" for the expression of a chemokine using the Sendai virus vector. Moreover, could one skilled in the art have reasonably predicted from the Yu and Bluel references

[2] See, for example, Office Action mailed April 14, 1999, page 5.

that a chemokine gene-carrying Sendai virus could express "a substantial amount of biologically active chemokine" as required by the claims?

Regarding the "motivation to select" issue, Yu clearly describes that while some proteins can be successfully expressed in a Sendai virus (e.g., gp120), others clearly cannot (e.g., firefly luciferase). As noted in Applicants' previous correspondence, the lack of firefly luciferase expression is not a function of the protein itself but a function of the specific vector used to express the protein, demonstrating that Sendai virus may not be appropriate for expressing all proteins. Dr. Inoue's comparative results conclusively establish this principle as well (see accompanying Declaration). Given the failings of Yu to express luciferase, as well as general failings of the art to provide an efficient means for producing recombinant chemokines,[3] one of ordinary skill at the art would not have been motivated to select Sendai virus vectors for recombinant chemokine expression.

Moreover, the claims require expression of a "substantial amount of biologically active chemokine." Nothing in the Yu reference discloses or suggests that a Sendai virus vector may be used to express large quantities of biologically active chemokines. Indeed, Applicants' unexpected success could not have been reasonably predicted from the Yu reference.

Regarding the "reasonable expectation of success" issue, Applicants again note that while the expression of gp120 using a Sendai virus vector was achieved, Yu failed to

[3] See, e.g., U.S. Patent No. 4,929,700 (copy enclosed), which discloses a process for obtaining recombinant human chemokine, CSF-1, expressed in *E. coli*, wherein the process requires extensive, multiple purification steps: (1) recovering CSF-1 as an insoluble protein from *E. coli* expressing CSF-1, (2) solubilizing the insoluble protein in a chaotropic environment and under reducing conditions, and (3) refolding the solubilized protein by removing chaotropic environment.

successfully produce a substantial amount of biologically active firefly luciferase using the same Sendai virus vector. One skilled in the art reading the Yu article would reasonable understand that the ability to successfully express a protein using the Sendai virus vector system was far from clear. Thus, contrary to the Examiner's assertion, Yu and Bluel do not provide a "reasonable expectation of success" for developing an expression vector or a method of synthesizing a biologically active chemokine using a Sendai virus.

In addition, Applicants direct the Examiner's attention to accompanying Declaration of Dr. Makoto Inoue, which addresses the Office's concerns regarding the "details necessary to fully evaluate the data presented," particularly experimental variables such as how the amounts of the factors were quantified (substantial vs. insubstantial amount?), characterization of the expressed proteins (Were the proteins biologically active?), similarities and differences between the vectors, cells used for each factor, and the like. As attested by Dr. Inoue, the expression levels of a protein using a Sendai virus vector cannot be predicted *a priori*. In particular, Dr. Inoue demonstrates that the production efficiency of two proteins, nerve growth factor (NGF) and glial cell line-derived neurotophic factor (GDNF) was examined using the recombinant Sendai Virus vector expression system. Using this expression system, Dr. Inoue attests that NGF was produced 60,000 to 80,000 times better than GDNF. Moreover, Dr. Inoue attests that the exogenous gene not affect the replication of the Sendai virus. Indeed, Dr. Inoue concludes that exogenous proteins encoded by the recombinant Sendai virus can be made

at vastly different levels and that the influence of the exogenous gene on the production efficiency of proteins, when using any given viral vector-protein combination, cannot be predicted. Furthermore, Dr. Inoue notes that not only was the NGF protein found to be biologically active, but also that a "substantial amount" of NGF (10.5 μg/ml) was produced.

Finally, the Office has failed to explain, when analyzing the references made of record, what specific understanding would have suggested the combination of references relied on by the Office. Instead, the obviousness analysis in the Office Action is limited to a discussion of how the references can be pieced together to yield the claimed invention. As the Federal Circuit stated in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985):

> It is an error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint." When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.

To believe that one skilled in the art would be motivated to construct and employ Applicants' disclosed Sendai virus chemokine vector expression system, when Yu and Bluel, either alone or in combination, never even discuss, suggest, or mention instructions for expressing a chemokine using a Sendai virus vector expression system in a way that would lead one to Applicants' invention for expressing a substantial amount of biologically-active chemokine, is to assume a level of inspiration constituting inventive activity. The case law makes clear that to avoid a hindsight-based obviousness analysis

that the Patent Office bears the burden of elucidating factual teachings, suggestions, or incentives from the prior art that show the suitability of the combination of references. *See Graham v. John Deere Co.*, 383 U.S. 1, 18, 148 U.S.P.Q. 459, 467 (1966) ("strict observance" of factual predicates to obviousness conclusion required). For all of the above-mentioned reasons, this burden has not been met and the rejection of the claims under § 103(a) for obviousness over these references should therefore be withdrawn.

CONCLUSIONS

Applicants submit that all of the claims are now in condition for allowance, such action being respectfully requested.

Marked-up versions of the amended claims and clean versions of all pending claims, reflecting entry of the amendments, are enclosed.

Also enclosed is a petition to extend the period for replying for three months, to and including December 5, 2001.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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